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| 09/810,521 | 03/19/2001 | Caroline Kreutzer | P 278416 980183 BT-CIP | 6186 |

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| EXAMINER |
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STEADMAN, DAVID J

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| ART UNIT | PAPER/NUMBER |
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1652

DATE MAILED: 04/18/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Applicant(s)

09/810,521

Applicant(s)

KREUTZER ET AL.

Examiner

David J. Steadman

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 19 March 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☒ The proposed amendment(s) will not be entered because:
- (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: see attachment.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☒ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: 16.

Claim(s) objected to: 22 and 23.

Claim(s) rejected: 1,3 and 27-32.

Claim(s) withdrawn from consideration: 5-15,17,18,21 and 24-26.

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
10. ☒ Other: interview summary

ADVISORY ACTION

- [1]** Claims 1, 3, 5-18, and 21-32 are pending in the application.
- [2]** Claims 1, 3, and 27-32 stand finally rejected.
- [3]** Claims 22 and 23 are objected.
- [4]** Claim 16 is in condition for allowance.
- [5]** Claims 5-15, 17, 18, 21, and 24-26 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.
- [6]** The request for reconsideration in the after final amendment of Paper No. 21, filed 03/19/03, is acknowledged. The amendment would appear to overcome the objections and partially overcome the rejection under 35 USC 112, second paragraph, as described in detail below. However, the amendment does not place the claims in condition for allowance because the amendment would require further consideration of the claims as a new objection and new rejections under 35 USC 112, second paragraph, would be required (see item 11 below). See MPEP 714.13 regarding non-entry of after final amendments.
- [7]** The objections to claims 1, 3, 22, 23, 27, 28, and 30-32 are maintained for the reasons of record and the reasons set forth below. Applicant argues (page 3 of Paper No. 21) the objections are overcome by amendment. However, in view of the non-entry of the amendment, the objections are maintained for the reasons of record. It is noted that the amendment would appear to overcome the objections.
- [8]** The rejection of claims 1, 3, 4, and 27-32 under 35 USC 112, second paragraph, is maintained for the reasons of record and the reasons set forth below. Applicant argues (page 4 of Paper No. 21) the rejections are overcome by amendment. However, in view of the non-entry of the amendment, the rejections are maintained for the reasons of record. It is noted that the amendment would appear to overcome the rejection to claims 1, 3, 4, and 28. It is noted that the amendment would not appear to overcome the rejection of claims 27 (claim 28 dependent therefrom) and 30-32 as applicant has not incorporated those changes as stated at page 4, lines 11-16, into the claims. Such changes would appear to overcome the rejection. It is further noted that the amendment would not appear to overcome the

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rejection of claim 29 as it is unclear from the specification and the claim as to whether the *dapA* gene is inserted within the coding sequence of an *aecD* gene or is fused to an *aecD* coding sequence. From the specification, it appears the *dapA* gene is *linked* to an *aecD* gene (pages 31-33 of the instant specification) and not inserted *into* an *aecD* gene.

[9] The written description and scope of enablement rejections of claims 1, 3, 27, 28, and 30-32 under 35 U.S.C. 112, first paragraph, are maintained for the reasons of record and the reasons set forth below. Applicant argues (beginning at page 4 of Paper No. 21) *C. glutamicum* *pyc*, *dapA*, *lysC*, and *lysE* genes are well known in the art and the amended claims are adequately described and the scope of the claims is fully enabled. However, in view of the non-entry of the amendment, the rejections are maintained for the reasons of record. It is noted that the amendment would appear to overcome the rejections to claims 1 and 3. It is noted that the amendment would not appear to overcome the rejections to claims 27, 28, and 30-32. Addressing the written description rejection, the specification discloses at page 7 that overexpression of a gene may be achieved by mutating the promoter and regulatory region or the ribosome binding site located upstream from the structural gene. Such structures of a genus of *C. glutamicum* *pyc*, *dapA*, *lysC*, and *lysE* overexpressing genes having mutations of the promoter, regulatory region, and/or ribosome binding site have not been disclosed in the specification. While sequences encoding wild-type *pyc*, *dapA*, *lysC*, and *lysE* gene products are known in the art, the prior art does not adequately describe a representative number of the recited gene structures, including *pyc*, *dapA*, *lysC*, and *lysE* genes having mutations of the promoter, regulatory region, and/or ribosome binding site. Furthermore, the structures of a genus of *lysC* genes resulting in an aspartate kinase that is resistant to inhibition and/or threonine have not been disclosed in the specification. The structures of the mutant genes are an essential feature of the claimed invention and should therefore be adequately described in the specification. Given the lack of description of representative species encompassed by the genera of genes recited in the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention. Addressing the scope of enablement rejection, as previously stated

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in Paper No. 18, the specification fails to disclose the alteration(s) to a *pyc*, *dapA*, *lysE*, or *lysC* gene resulting in overexpression of said genes or, in the case of *lysC*, encoding an aspartate kinase that is resistant to inhibition and/or threonine. As stated above, while sequences encoding *C. glutamicum pyc*, *dapA*, *lysC*, and *lysE* gene products are known in the art, the prior art does not provide guidance as to those alterations of *C. glutamicum pyc*, *dapA*, *lysC*, and *lysE* genes, including mutations of the promoter, regulatory region, and/or ribosome binding site that will successfully achieve the desired overexpression. Without such guidance, one of skill in the art would be required to analyze each gene's promoter, regulatory regions, and ribosomal binding sites (if known in the art or identify said promoter, regulatory regions, and ribosomal binding sites if not known) for nucleotides that may be altered in order to obtain overexpression. In the case of *lysC*, one must further determine nucleotides that may be substituted to obtain an encoded aspartate kinase having feedback resistance to inhibition and/or threonine. Based on the guidance provided in the specification, it is highly unpredictable as to which of the nucleotides of a recited gene may be altered with an expectation of obtaining *C. glutamicum* bacteria overexpressing the recited genes or, in the case of *lysC*, overexpressing a feedback resistant aspartate kinase. As such, one of skill in the art would recognize that a large quantity of experimentation is necessary to make the broad scope of claimed L-lysine-producing *C. glutamicum* bacteria.

[10] The rejection of claims 30 and 31 under 35 U.S.C. 103(a) as being unpatentable over Peters-Wendisch et al. (IDS reference OR; DE 19831609) in view of Cremer et al. (IDS reference QR; EP 0435132), Vrljic et al. (IDS reference PR; DE 19548222), and Araki et al. (IDS reference RR; EP 0854189) is maintained for the reasons of record. Applicant argues (beginning at page 5 of Paper No. 21) the cited references do not teach or suggest simultaneous enhancement of *pyc*, *dapA*, and *lysE* genes or *pyc*, *dapA*, *lysC*, and *lysE* genes via use of the *dapA* promoters of SEQ ID NO:5 or 6. However, in view of the non-entry of the amendment, the rejections are maintained for the reasons of record. It is noted that the amendment would not appear to overcome the rejection as the claims are not so limited to recite the *dapA* promoter of SEQ ID NO:5 or 6. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26


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USPQ2d 1057 (Fed. Cir. 1993). The cited references teach all claim limitations, provide a motivation for making the claimed bacterium, and enable the claimed invention. Thus, the cited references meet the three basic criteria to establish a *prima facie* case of obviousness over claims 30 and 31.

[11] Regarding a new objection and rejections under 35 USC 112, second paragraph, the following comments are provided: a new objection would be required for inconsistent use of "lysE" and "LysE" in claim 3 and new rejections under 35 USC 112, second paragraph, would be required for the use of "LysE genes" in claim 3 and for lack of antecedent basis in the recitation of "said overexpressed aspartate kinase" in claim 32.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Thursday from 6:30 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652


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